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EDITORIAL

# Physiological interventions in cardiac arrest: passing the pilot phase

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The damaging processes leading to a poor outcome after cardiac arrest start at the onset of ischemia and continues during the reperfusion phase. Intensive care treatment in resuscitated patients relies on organ support restoring normal physiology with attention to brain protection. Drugs have not proven beneficial in randomised trials. To date induced hypothermia, or targeted temperature management (TTM), is the only specific intervention implemented in clinical practice. Nevertheless, its final role and configuration are still under debate and are currently being investigated.

Easily modifiable clinical physiological and metabolic parameters could be ideal treatment candidates to possibly attenuate brain damage. In a pilot trial, strict glucose control was tested versus standard care with no significant difference in the outcome, and the concept has not been further challenged [1]. In recent years three possible physiological candidates have been investigated in several observational cohorts indicating better outcome with higher mean arterial pressure (MAP), moderately elevated partial pressure of oxygen ($PaO_2$) and mildly elevated partial pressure of carbon dioxide ($PaCO_2$) [2–4]. Other reports have indicated worse outcome with increasing doses of vasopressors, hypotension, hypocapnia, severe hypercapnia and severe hyperoxia [5–7]. Also, completely neutral reports have been published [8]. A pilot trial of mild hypercapnia versus normocapnia (standard care) suggested better outcome and lower levels of biomarkers of brain damage with mildly elevated carbon dioxide levels [9]. The well-known limitations of observational inferences have called for randomised trials.

In this issue of *Intensive Care Medicine*, a Finnish/Danish group has, in two publications, reported an elegant 2 × 3 factorial multicentre pilot trial in 123 comatose cardiac arrest patients—the COMACARE trial. The patients were randomised to one of eight groups with either high or low normal MAP, high or low normal $PaCO_2$ and normal or moderately elevated $PaO_2$. Being a pilot trial feasibility was an important outcome and the authors demonstrated clear and distinct separation between the groups for MAP, $PaO_2$ and $PaCO_2$. The primary effect outcome was serum level of neuron specific enolase (NSE) at 48 h after the arrest, a time point where this prognostic biomarker of brain damage separates good from poor outcome. Interestingly there were no detectable differences in 48-h NSE for any of the three interventions, and secondary outcomes such as NSE over time, the biomarker S100B, cardiac troponin, global electroencephalographic pattern, survival and functional outcome at 6 months were also neutral. The overall outcome was strikingly good for a cardiac arrest cohort and it is worth emphasizing that the patient group was positively selected in terms of age, initial rhythm and a presumed cardiac cause of the arrest. The single statistically significant finding was higher cerebral oxygen saturation, up to approximately 10% absolute difference, with higher levels for high normal $PaO_2$ and $PaCO_2$ and with the figures suggesting more difference for $PaCO_2$ than $PaO_2$. Vasodilation due to elevated $PaCO_2$ and increased cerebral blood flow (CBF) may thus be more powerful in terms of increasing oxygen delivery with the chosen intervention targets. In this trial CBF was, however, not measured and its correlation to regional cerebral saturation is not fully elucidated. Since oxygen content typically increases marginally between 10 and 25 kPa and the content of oxygen in blood is more influential on CBF than $PaO_2$, it

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is reasonable not to expect a tremendous effect on CBF or cerebral saturation with the oxygen intervention in this trial [10]. Importantly the changes in cerebral saturation were not translated to any other outcome differences. Higher MAP did not influence cerebral saturation (or any other outcome), perhaps because of the adequate cerebral perfusion pressure obtained already at the low normal level of MAP. In contrast, a recent randomised trial, presented at American Heart Association 2018, did report that a higher target MAP (85–100 mmHg) improved cerebral perfusion and oxygenation [11]. Signs of anoxic brain damage on magnetic resonance imaging and functional outcome were, however, neutral.

NSE has been used as a surrogate outcome in several cardiac arrest trials as it is a good discriminator of poor and good outcome [12]. A considerable drawback with NSE is the sensitivity to haemolysis due to leakage of NSE from red blood cells [13]. The authors report that seven analyses were excluded as a result of haemolysis and only one sample at the 48-h primary outcome. However, haemolysis was only analysed in one of the participating countries and the cut-off level for exclusion due to haemolysis was very high (>500 mg free haemoglobin/L). A value of 300 mg/L is already considered visible haemolysis, and NSE levels are heavily influenced at much lower degrees of haemolysis and dependent on the relationship between NSE and haemolysis [14]. With lower serum levels of NSE little haemolysis can be tolerated, while with higher levels more haemolysis is tolerated. With the modest median levels of NSE reported in this trial a much lower cut-off level for exclusion due to haemolysis should have been employed, and significant haemolysis was therefore likely higher than reported. The influence on the trial results are difficult to appreciate. Reassuringly, NSE findings were in line with all other outcomes and the levels were not used for prognostication but for comparison between groups. For future trials, other biomarkers such as protein-tau or neurofilament, not or less sensitive to haemolysis, may prove better surrogate outcomes [15].

A common critique of clinical trials includes questions of timing and dose of the intervention. In this trial the interventions were introduced immediately after emergency randomisation with deferred consent. In light of other trials in which manipulating oxygen levels in the ambulance was associated with problems with hypoxia [16], that airways are often not secured prior to hospital admission, and that the initial phase after return of spontaneous circulation seldom allows for fine tuning of haemodynamics, the 3-h median delay seems difficult to shorten and likely will reflect clinical practice if any of the interventions are implemented. The authors designed the trial elegantly, randomising to extremes of normal levels for two of the three target interventions, and thus most of the patients were treated within standard care. Although statistically different, the interventions may thus have been separated too little to produce a meaningful clinical difference. Also, the trial was indeed a pilot with a very optimistic predefined power calculation (50% reduction of NSE) and a larger trial may very well have indicated more robust signals. The main and important conclusion of the COMACARE trial must be that the targets can be readily obtained for all three interventions and that adequately powered trials may follow, in which carbon dioxide manipulation possibly has the most intriguing physiological rationale.

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